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Sensory feedback signal derivation from afferent neurons

Contract No.: **NIH-NINDS-NO1-NS-3-2380**

QUARTERLY PROGRESS REPORT #8

for the period

1 Sept. 1994 -- 30 Nov. 1994

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Date of submission of this report: 19 Jan. 1995

I. Summary of the Overall Project

In this study we are exploring the feasibility of extracting 1) cutaneous sensory information about fingertip contact and slip, and 2) proprioceptive sensory information about wrist or finger position. We use implanted nerve cuff electrodes to record peripheral nerve activity in animal models.

Our overall **objectives** for the 3-year duration of this contract are as follows:

1. Investigate, in cadaver material, implantation sites for nerve cuff electrodes from which cutaneous and proprioceptive information relevant to the human fingers, hand and forearm could be recorded.
2. Select a suitable animal preparation in which human nerve dimensions and electrode placement sites can be modeled and tested, with eventual human prosthetic applications in mind.
3. Fabricate nerve cuff electrodes suitable for these purposes, and subcontract the fabrication of nerve cuff electrodes of an alternate design.
4. Investigate the extraction of information about contact and slip from chronically recorded nerve activity using these animal models and electrodes. Specifically,
   a. Devise recording, processing and detection methods to detect contact and slip from recorded neural activity in a restrained animal;
   b. Modify these methods as needed to function in an unrestrained animal and in the presence of functional electrical stimulation (FES);
   c. Record activity for at least 6 months and track changes in neural responses over this time.
5. Supply material for histopathological examination from cuffed nerves and contralateral controls, from chronically implanted animals.
6. Investigate the possibility of extracting information about muscle force and limb position from chronically recorded neural activity.
7. Cooperate with other investigators of the Neural Prosthesis Program by collaboration and sharing of experimental findings.

II. Summary of Progress in the Eighth Quarter

During the eighth quarter, four of our Year Two subjects surpassed the 180 day implant period milestone. We continued to monitor the stability of compound action potentials under anesthesia and recorded voluntary nerve and muscle activity in six Year Two subjects, and we initiated the post-mortem histopathological examination of nerves in one of them. The remaining three post day-180 subjects were very successful at performing voluntary tasks and we continued to record from them. We recorded nerve and muscle activity during a 1-dimensional forelimb task, and we made progress towards completing the computer-controlled forelimb task hardware and control software. We also continued communications with our collaborators in applying intelligent algorithms to analyze and predict nerve and muscle signals recording during walking on a treadmill. Finally, we presented preliminary results of our investigations at the semi-annual meeting of the Alberta Motor Control group in Kananaskis, Alberta, Sept. 1994, and at the 25th annual Neural Prostheses Workshop in Bethesda, Maryland, Oct. 1994.

III. Details of Progress in the Eighth Quarter

A. Status of Year Two implants on Nov. 30, 1994

Two nerves were instrumented in each of six Year Two cats. We periodically monitored compound action potentials (CAPs) in order to evaluate the status of the nerve and recording devices. Progress Report #2 provided a description of the stimulation and recording protocols for monitoring CAPs. Table 1 summarizes the CAP data for each of the six implants in terms of number of days implanted and nerve CAP amplitude recorded form the distally placed cuff relative to day 0. Although the first four Year Two implants surpassed our 180 day implant period goal, we performed only one final acute this quarter (NIH 10 on day 204), as we are continuing to monitor CAPs and behavioural tasks in the five other implants.

TABLE 1. Year Two data summary as of Nov. 30,1994

Subject	Total Days implanted	Problems with Implanted Cuffs Median	Ulnar	Radial	Final Nerve CAP Amplitude Median %, last day	Ulnar %, last day	Radial %, last day
NIH 9	217	prox cuff replaced on day 35			20%, 188	40%, 188	
NIH 10	204 FA				108%, 204	117%, 204	
NIH 11	196				116%, 180	60%, 180	
NIH 12	189			prox wires broken after day 75	100%, 181		prox wires broken after day 75 106%, 75
NIH 13	160					92%, 146	124%, 146
NIH 14	153					124%, 139	184%, 139

As of Nov. 30, we successfully recorded CAPs from 92% (11/12) of the implanted nerves, compared to a success rate of 60% (9/15) at the same stage last year (near day 180 for the last implant).

As discussed in Progress Report 7, a single case of broken wires occurred in NIH 12, but even in that case there appears to be no nerve damage from pulled wires, based on normal recordings from the distal Radial nerve cuff in,the awake cat.

Progress reports 4 and 7 summarized the problems that occurred with our Year One series of implants and the corrections to these problems that we implemented in Year Two. To date, we are very pleased with the improved longevity of the implanted devices and associated hardware such as subcutaneous wires, backpack connections and backpack sutures.

Note that we replaced the proximal Median cuff in NIH 9 on day 35 following a steep decline in CAP amplitude. The amplitude has since recovered from < 1% to approximately 20% of the initial (day 2) amplitude. The average CAP amplitude of the 10/12 nerves shaded in Table 1 that have not suffered an obvious injury from initial compression or pulled wires is 107% ± 37% (1 SD), which suggests that the instrumented nerves are healthy and have not suffered significant trauma.

B. CAP data of four Year Two implants that reached day 180 prior to Nov. 30, 1994

In the quarter ending Nov. 30, 1994, four of our Year Two subjects surpassed the 180 day implant milestone, with excellent results. Figure 1 below presents the amplitudes of CAPs recorded from distal nerves in cats 9, 10, 11, and 12 up to a period of 180 days, normalized with respect to day 0. These data have been interpolated at 30 day intervals for comparative purposes, based on the actual data recorded from each cat. Seven data plots are displayed which correspond to the seven nerves described in Table 1 (the exception is the Radial nerve in NIH 12). Only one nerve, the Median nerve in NIH 9 (small square symbols in Fig. 1), showed a steep decline in CAP amplitude following implant. An exploratory surgery on day 35 revealed that this nerve had been compressed by the proximal cuff. The cuff was removed and a second, larger diameter cuff was implanted at that time. As is seen in Figs. 1 and 2, the nerve slowly recovered throughout the rest of the implant period.

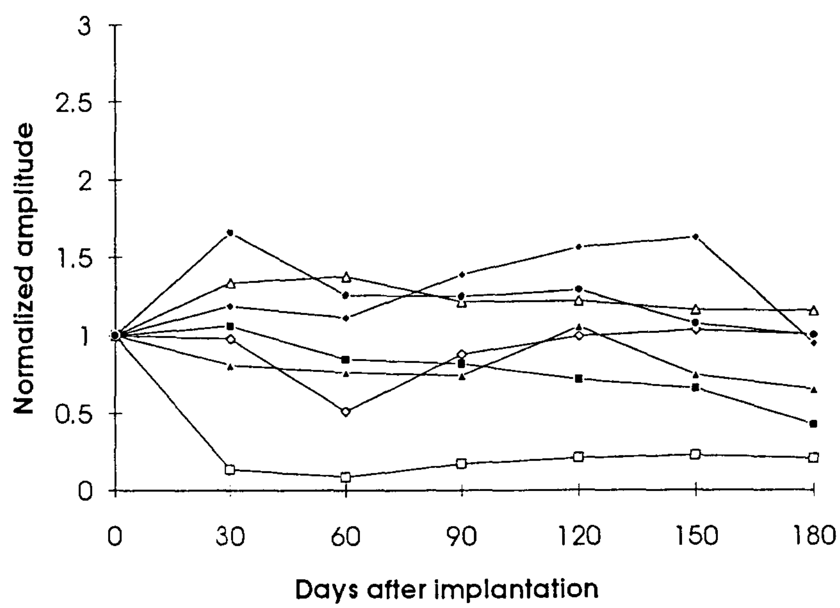

Figure 1: Normalized peak-peak amplitudes of distal CAPs (normalized at day 0; n = 7; cats 9,10,11,12)

The corresponding nerve conduction times between stimulating and recording cuffs are shown in Fig. 2 in the form of normalized time to the first positive peak of the CAP. The CAP latency data shows very little variability, which emphasizes that the fastest (and therefore the largest and most vulnerable to compression neuropathy) fibres in the nerve have not suffered as a result of instrumentation. The greater variability observed for CAP amplitude data (Fig. 1) than for latency data (Fig. 2) emphasizes the fact that the amplitude recorded by a tripolar nerve cuff is in part determined by connective tissue ingrowth and gradual electrode impedance changes throughout the implant period (Stein et. al, 1978).

Note that the drop in CAP amplitude in the damaged Median nerve in NIH 9 corresponds with a substantial rise in conduction time for the same nerve (small square symbols in Fig. 2), a trend that then slowly reversed as the axons recovered from the compression injury.

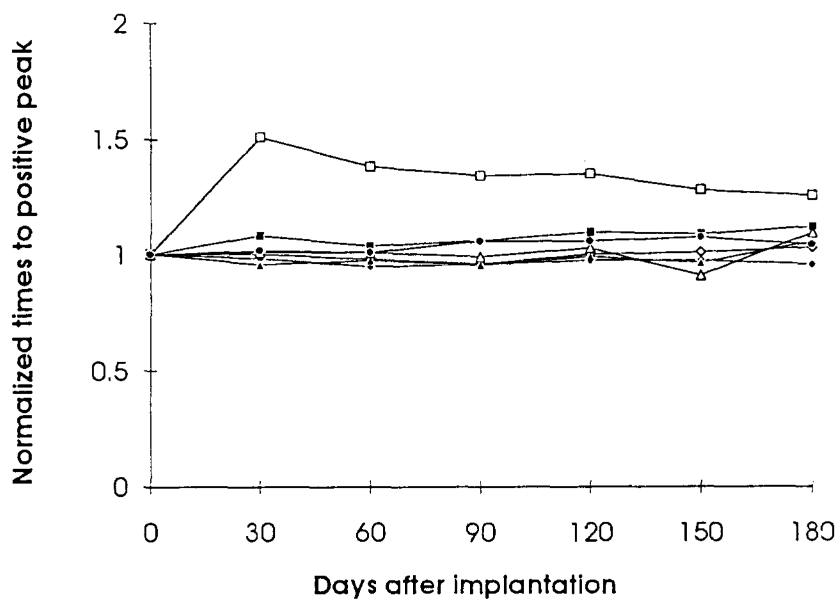

Figure 2: Normalized times to first positive peak of distal CAPs (normalized at day 0; n = 7; cats 9,10,11,12)

Figures 3 and 4 present the averages of the normalized CAP amplitude and conduction time data shown in Figs. 1 and 2 respectively, with the omission of the Median nerve data from NIH 9 that had suffered the compression injury. The average CAP amplitude remained stable throughout the entire implant period, not deviating from the initial CAP amplitude at day 0 by more than 17% (at day 30). The maximum standard deviation of the CAP amplitudes at any point in the implant period was 34% (at day 150). These results were much better than our Year One results from 9 implanted nerves in 8 cats, where we observed a maximum average deviation throughout the implant period of 29% (at day 90) and a maximum standard deviation at any point in the implant period of 74% (also at day 90). Please refer to Progress Report #5 for a complete summary of our Year One implant CAP results.

Figure 4 reflects the minimal spread in the CAP conduction latency as shown in Fig. 2 with a very stable average (maximum deviation from day 0 average of 5% at day 150) and a maximum standard deviation at any point in the implant period of 7% (at day 180). We are very pleased with the evident stability of instrumented nerves and cuffs as evidenced by the CAP recordings in the four Year Two implants that have reached the day 180 milestone.

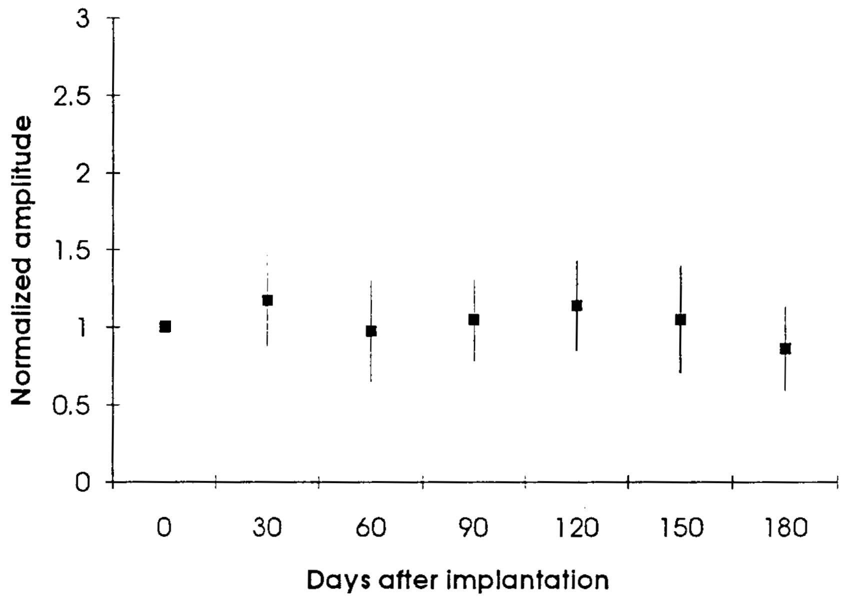

Figure 3: Average peak-peak amplitude of distal CAPs ± 1 SD
(normalized at day 0; n = 6; cats 9,10,11,12)

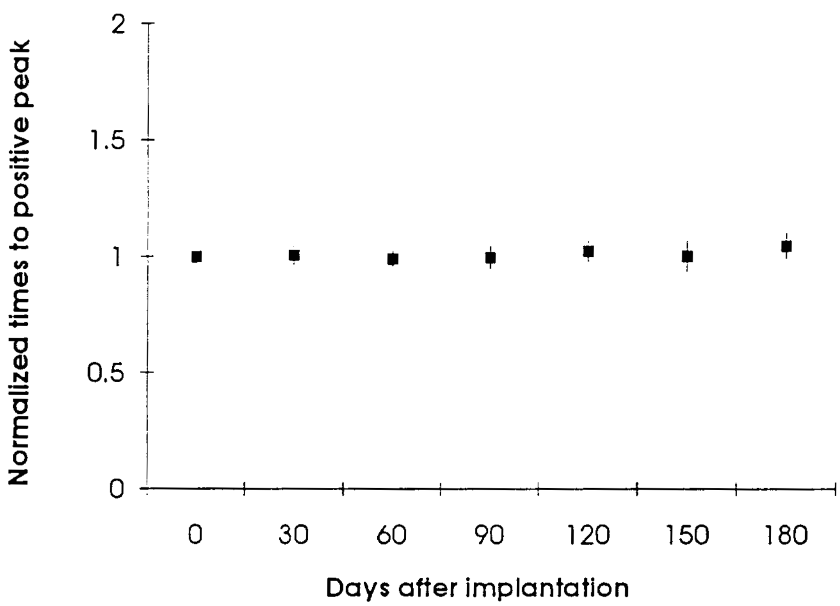

Figure 4: Average time to first positive peak of distal CAPs ± 1 SD
(normalized at day 0; n = 6; cats 9,10,11,12)

C. Analysis of ENG and EMG activity patterns during behavioural tasks

During the eighth quarter we continued collecting nerve and muscle activity data from the six cats, during walking on a treadmill and during a 1-D passive forelimb reaching and grasping task. The ENG signals from the distal nerve cuffs and the EMG signals from four implanted forelimb muscles were bandpass filtered to minimize noise, amplified to suitable levels, and stored on FM tape for off-line analysis. The off-line analysis includes sampling (10 kHz for ENG and 1 kHz for EMG), and digitally rectifying and smoothing the signals to produce relatively clean waveforms. To date we have used Matlab to analyze the ENG signals in terms of timing relative to distinct events and phases during the tasks and in terms of predicting the simultaneously recorded EMG activity. Progress Report #7 provided examples of data recorded during walking on the treadmill and during the forelimb reaching and grasping task.

As mentioned in Progress Report #7, we have initiated parallel collaborations with Dr. Dejan Popovic and Zoran Nicolic at the University of Miami, and with Dr. Dick Stein and Aleks Kostov at the University of Alberta to implement automatic rule-generating algorithms in the analysis of nerve and muscle data recorded in the cat forelimb during walking. To this end, we have collected data and investigated methods of processing it to provide useful inputs for the analysis algorithms. The processing includes bin integration and resampling at a much lower frequency to reduce the total amount of data for automatic analysis without losing the overall information of both the nerve and muscle signals.

D. Acute recordings and preparation of samples for histopathological examination of NIH 10

Final acute recordings and preparation of samples for histopathological examination were performed on NIH 10 on day 204. This particular cat did not perform well at the forelimb task and, as we had collected sufficient data during walking on a treadmill and he had surpassed 180 days, he was sacrificed. Recording cuffs had been implanted on the Ulnar and Median nerves, and the final CAP recordings shown in Table 1 provide evidence that both the nerves and the cuffs remained quite stable throughout the implant period. The awake recordings of nerve and muscle activity during walking also supported the assessment that the nerves were healthy throughout the whole implant period. Visual examination of the nerves and cuff electrodes further showed that the nerves were of normal colouration and healthy, and that the nerve cuffs were well aligned and encapsulated with a fine layer of healthy, clear connective tissue. Samples of the instrumented nerves were taken for histological analysis.

Prior to sacrifice of NIH 10, we performed final CAP recordings that included electrical stimulation of the cutaneous fibres of each digit as described in Progress Report #5. The cutaneous fields of the Ulnar and Median nerves agreed with our findings in the first series of implants.

E. Improved cuff designs

The final acute findings in NIH 10 were in contrast to the Year One implants, where we had often observed large amounts of discoloured connective tissue surrounding nerve cuffs, which we have partially attributed to the use of sutures to close the cuffs. Sutures may absorb contaminants during the manufacturing process which may initiate local tissue reactions around the cuff. In addition, we observed that in long term implants, many of the suture knots used to close nerve cuffs had actually disintegrated or come undone after a period of six months, which could lead to opening of the cuff and even electrode migration.

During Year two, we implemented a novel cuff closing mechanism, aspects of which were reported in Progress Report #4. This design has eliminated the use of sutures to close the cuffs and has resulted in a safer and more reliable method of installing cuffs around nerves that appears less prone to promote local tissue reactions. In the eighth quarter we initiated patent applications concerning improvements in cuff designs, details of which will be disclosed in future reports.

F. Development of forelimb task hardware

We continued to develop the computer-controlled forelimb task hardware, concentrating on the feedback systems to include force feedback to improve control of joystick stiffness during the task, and on including an automated food reward system and an intelligent task triggering switch. We have experienced some delay in the hardware development due to personnel changeover from David Viberg to Dr. Yunquan Chen in the latter part of this quarter. However, Dr. Chen has a most appropriate background in electrical and biomedical engineering, and his addition to our group has already been beneficial to this project in several aspects.

G. Reporting results at meetings

During the eighth quarter, we attended two meetings and presented preliminary data collected during walking and forelimb reaching and grasping tasks. The first conference was a semi-annual meeting of the Alberta Motor Control group in Kananaskis, Alberta in Sept. Kevin Strange presented an overview of the NIH project along with preliminary data. The second session was the 25th annual NIH Neural Prostheses Meeting in Bethesda, Maryland in Oct., where Andy Hoffer, Klaus Kallesøe, and Kevin Strange provided updates on the previous year's activities and scientific accomplishments.

/. Plans for Ninth Quarter

In the ninth quarter we intend to:

1. examine histopathologically the nerves from Year One cats (objective 5)
2. continue recording Year Two cats on treadmill and forelimb tasks (objective 4a)
3. design and construct cuffs appropriate for smaller proprioceptive nerves (objective 3)
4. continue monitoring status of Year Two implanted nerves and electrodes (objective 4)
5. complete the histopathological examinations of Year Two cats (objective 5)
6. complete the construction of an 8-channel stimulator to be used for FES of forelimb muscles (objective 4b)
7. complete the construction of hardware and begin the software design for controlling the reaching task (objective 4a,b)

V. References

Stein, R.B., Charles, D., Gordon, T., Hoffer, J.A. and Jhamandas, J. Impedance properties of metal electrodes for chronic recording from mammalian nerves. *IEEE Trans. BME* 25: 532-537, 1978.